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THE HEMODIALYSIS INDUCED BLOOD GLUTAMATE REDUCTION IN CHRONIC RENAL FAILURE: POTENTIAL IMPLEMENTATION FOR NEUROPROTECTION

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ГЕМОДИАЛИЗ-ИНДУЦИРОВАННОЕ СНИЖЕНИЕ УРОВНЯ ГЛУТАМАТА В КРОВИ ПРИ ХРОНИЧЕСКОЙ ПОЧЕЧНОЙ НЕДОСТАТОЧНОСТИ: ПОТЕНЦИАЛЬНАЯ РЕАЛИЗАЦИЯ НЕЙРОПРОТЕКЦИИ

Цель. Целью работы является исследование возможности гемодиализа (HD) быть эффективным в снижении уровня глютамата в крови. Кроме того, изучали влияние HD на уровни глутамата оксалоацетатной трансаминазы (GOT) и глутаматпируват-трансаминазы (GPT) в крови и описывали скорость и структуру клиренса глутамата в крови во время HD.

Материал и методы. Образцы крови были взяты у 45 пациентов с хроническим заболеванием почек V стадии сразу после начала HD с почасовым контролем в течение 5 ч. Образцы были отправлены для определения уровней глутамата, глюкозы, GOT, GPT, гемоглобина, гематокрита, мочевины и креатинина. Образец крови от 25 здоровых добровольцев без хронической почечной недостаточности использовался в качестве контроля для определения исходных уровней глутамата в крови, GOT и GPT.

Результаты. Содержание глутамата и GPT у пациентов с HD было выше на исходном уровне по сравнению со здоровым контролем ($p<0,001$). В первые 3 ч после HD наблюдалось снижение содержания глутамата в крови по сравнению с исходными уровнями ($p<0,00001$). На 4-й час наблюдалось увеличение уровня глутамата в крови по сравнению с 3-м часом ($p<0,05$).

Выводы. HD может быть многообещающим методом снижения уровня глутамата в крови.

Ключевые слова: травма головного мозга; глутамат; глутаматная оксалоацетатная трансаминаза (GOT); глутаматпируват-трансаминаза (GPT); гемодиализ.

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THE HEMODIALYSIS INDUCED BLOOD GLUTAMATE REDUCTION IN CHRONIC RENAL FAILURE: POTENTIAL IMPLEMENTATION FOR NEUROPROTECTION

Purpose. The purpose of the present study is to investigate whether hemodialysis (HD) may be effective in lowering blood glutamate levels. Additionally, we examined the effect of HD on glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT) levels in the blood and describe the rate and pattern of blood glutamate clearance during HD.

Material and methods. Blood samples were taken from 45 patients with stage V chronic kidney disease immediately after initiation of HD, and hourly for a total of 5 blood samples. Samples were sent for determination of glutamate, glucose, GOT, GPT, hemoglobin, hematocrit, urea and creatinine levels. A blood sample from 25 healthy volunteers without chronic renal failure was used as a control for the determination of baseline blood levels of glutamate, GOT and GPT.

Results. Glutamate levels and GPT levels in patients on HD were higher at baseline compared with healthy controls ($p<0.001$). In the first 3 hours after HD, there was a decrease in blood glutamate levels compared with baseline levels ($p<0.00001$). At the 4th hour, there was an increase in blood glutamate levels compared with the 3rd hour ($p<0.05$).

Conclusions. HD may be a promising method of reducing blood glutamate levels.

Key words: brain injury; glutamate; glutamate oxaloacetate transaminase (GOT); glutamate pyruvate transaminase (GPT); hemodialysis.

Introduction

Excitatory amino acids such as glutamate are released in high concentrations after head trauma and cerebral ischemia [1–4]. Previous studies in humans [5–7] and animals [4] have demonstrated that L-glutamate (glutamate) plays a crucial role in causing nerve damage after brain injury. It was shown that glutamate is toxic to nerve cells when released in large quantities [4]. Animal models demonstrated that glutamate receptor antagonists or substances that inhibit the release of glutamate can prevent or limit the neurological impairment processes. Those findings suggest that the neurological damage is associated with glutamate-induced excitotoxicity, and that the hyperactivity caused by the glutamate receptors is due to high and abnormal concentrations of glutamate [8–12].

There are glutamate transporters on the anteluminal side of endothelial cells in the brain capillaries [13; 14]. These transporters provide another route of glutamate removal from the brain [13; 15–17]. Gottlieb et al. demonstrated the very rapid appearance of radiolabeled glutamate in the blood after it was injected into rats' brain ventricular system [18]. In addition, they showed that the rate of glutamate flow from the brain to blood can be increased by creating a greater concentration gradient between the brain and blood fluids. Thus, an increased flow of glutamate from the brain to the blood can be achieved by reducing the level of glutamate in the plasma, thereby increasing the concentrations gradient of glutamate between the brain's extracellular fluids (ECF) and the blood [19–21]. Scavenging blood glutamate, by metabolizing glutamate into its inactive metabolite 2-Ketoglutarate, is possible by utilizing blood resident enzymes glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT). Administration of their corresponding co-substrates, oxaloacetate and pyruvate, respectively, has been shown to increase the flow of glutamate from ECF into the blood. This leads to decreased gluta-

mate levels in the brain, promoting neuroprotection [18–21]. Conversely, intravenous injection of glutamate into the blood decreases the driving force of glutamate out of the brain, and results in a worse neurological outcome [14; 19; 21; 22].

Hemodialysis (HD) may provide a method for decreasing blood glutamate levels after brain injury. In contrast to medicinal treatments with side effects and risks of toxicity, HD is a well-established and a widely-used method of filtering various substances from the blood. The purpose of the present study is to investigate whether HD may be effective in lowering blood glutamate levels, which may serve as a potential tool for improving neurological function after brain injury. Additionally, we examined the effect of HD on GOT and GPT levels in the blood.

The goals of this study were to compare blood glutamate, GOT and GPT levels in patients on HD compared with healthy controls, and to determine the effect of HD on blood glutamate, GOT, GPT and glucose levels in patient with chronic renal failure. Lastly, we describe the rate and pattern of blood glutamate clearance during HD.

Materials and methods

This experiment was conducted according to the recommendations set by the Helsinki Committee, and was approved by the Ethics Committee of Ben Gurion University of the Negev, Beer Sheva, Israel. Each subject signed an informed consent participation in the study.

Population

The control group included 25 healthy volunteers without chronic renal failure (CRF) aged 44 to 72 years. The HD group contained 45 patients with stage V chronic kidney disease on HD aged 22 to 88 years. The exclusion criteria included patient refusal or inability to obtain informed consent, severe anemia (Hb<7 g/dl), and age<18.

Study protocol

The following data was collected from medical records of HD patients: age, gender, time of dialysis treatment, type of HD fluid, type of dialyser, length of HD session, ultrafiltration rate, and the amount of ultrafiltrate removed during HD. Two types of dialysers were used in this study: Medium flux diameter filter (F8 HPS Fresenius Medical Care, flow of dialysate 500 ml/min) and High flux diameter filter ((FX80 Fresenius Helixone, HPS Fresenius Medical Care, flow of dialysate 800 ml/min). No reuse technique was performed in this study. Blood flow rate ranged between 250 and 300 ml/min. Blood samples were collected from the outflow branch using a stop-cock present on the tubing of the HD machine. Both arterio-venous fistula or tunneled dialysis catheters were used as indicated. Baseline blood samples were obtained immediately after initiation of HD. The last blood sample was obtained immediately prior to disconnection from the dialysis machine. Those blood samples were sent for determination of glutamate, glucose, GOT, GPT, Hb, Ht, urea, and creatinine levels. Blood samples for the determination of blood glutamate levels were collected additionally every hour throughout the entire experiment. The length of the dialysis was typically 4 hours; therefore 5 blood samples in total were obtained in the HD group. In the control group we collected only one blood sample for the determination of baseline blood levels of glutamate, GOT and GPT.

Blood sample analysis

Whole blood (200 μl aliquot) was deproteinized by adding an equal volume of ice-cold 1M perchloric acid (PCA) and then centrifuging at 10000×g for 10 min at 4°C. The

pellet was discarded and supernatant collected, adjusted to pH 7.2 with 2M K2CO3 and, if needed, stored at — 80°C for later analysis. Glutamate concentration was measured using the fluorometric method of Graham and Aprison [23]. A 20 μl aliquot from the PCA supernatant was added to 480 μl of a 0.3 M glycine, 0.25 M hydrazine hydrate buffer adjusted to pH 8.6 with 1M H_2SO_4 and containing 15 U of glutamate dehydrogenase in 0.2 mM NAD. After incubation for 30–45 min at room temperature, the fluorescence was measured at 460 nm with excitation at 350 nm. A glutamate standard curve was established with concentrations ranging from 0–6 μM. All determinations were done at least in duplicates.

GOT and GPT levels were determined in the biochemical laboratory of Soroka Medical Center via a fluorescent method (Olympus AU 2700). GOT and GPT levels were determined based on the conversion of glutamate into alanine and aspartate in the presence of GOT and GPT respectively.

Urea, creatinine and glucose levels were determined in the biochemical laboratory of Soroka Medical Center via a fluorescent method (Olympus AU 2700).

Statistical analysis

We hypothesized that the glutamate concentrations in the blood samples would differ for HD patients compared with the control group. Accordingly, this comparison was made with a t-test for independent values. The comparison between baseline and different time points for glutamate in HD patients was made with a general linear model. The comparison between baseline and end-points for GOT, GPT, hematocrit, urea, and glucose was made with a paired sample t-test. The effect of filter pores diameter and blood inflow on glutamate filtration was measured using Mauchly's test of specificity. The minimal level of significance accepted was $p<0.05$. Differences were considered as strongly significant when $p<0.01$. Data are presented as average ±SD or CI.

Results

The total number of participants, age, and gender distribution, as well as baseline levels of blood glutamate, GOP, and GPT in both study groups are presented in table 1. There were 45 patients in the HD group (19 women and 26 men) and 25 patients in the control group (9 women and 16 men). The average age in the control group was (57.79±3.43) years and (63.93±6.16) years in the HD group.

Baseline blood glutamate levels were found to be significantly higher in the HD patients compared with the control group ((392.87±34.80) μM/L vs. (178.49±41.21) μM/L respectively, $p<0.001$).

Subsequent measurements during the HD session demonstrated a significant decrease in blood glutamate levels compared to baseline levels at all the time points (fig. 1). By the fourth hour of HD, glutamate levels were significantly lower compared with baseline levels ($p<0.0001$). However, a statistically-significant increase in glutamate levels toward baseline was observed during the fourth hour of HD compared with the third hour ($p<0.005$).

Within the subgroups, the size of the filter pores and the rate of blood flow did not seem to significantly affect blood glutamate levels ($p>0.05$). No statistically-significant differences in blood glutamate levels were observed between men and women, although women demonstrated non-significantly higher blood glutamate levels compared to men at all time points.

Table 1

General Characterizations of HD Patients and Control

Value	HD Group (95% CI)	Control (95% CI)	Pv of Unpaired t-test
n	45	25	—
Number of females	19	9	—
Age	63.93±6.16	57.79±3.43	0.0725
Glutamate	392.8700±34.7962	178.49±41.21	<0.001
GPT	12.57±3.40	26.65±4.56	<0.001
GOT	20.05±3.15	23.99±2.55	0.085

Note. Total number of participants, age, gender distribution, and baseline levels of blood glutamate, GOP, and GPT in HD and control groups. Data is presented as mean ± standard deviation. Glutamate levels and GPT levels in patients on HD were significantly higher at baseline compared with healthy controls ($p<0.001$). GOT levels were non-significantly higher in patients on HD compared with healthy controls ($p=0.085$).

GPT levels in HD patients were significantly lower compared with the control group ((12.57±3.40) IU/L vs. (26.65±4.56) IU/L respectively, $p<0.001$). Similarly, HD patients had slightly lower levels of GOT compared with the control group, though this difference was not significant (20.05 IU/L vs. 23.99 IU/L respectively, $p>0.05$).

Table 2 presents the levels of blood glutamate, GOT, GPT, hematocrit, urea, creatinine, and glucose before and after HD. GOT levels were found to be significantly higher after HD ((20.05±10.20) IU/L pre-HD vs. (24.5±11.5) IU/L post-HD, $p<0.0001$). Similarly, GPT levels increased during HD (12.5±11.0 pre-HD vs. 15.1±12.6 post-HD, $p<0.0001$).

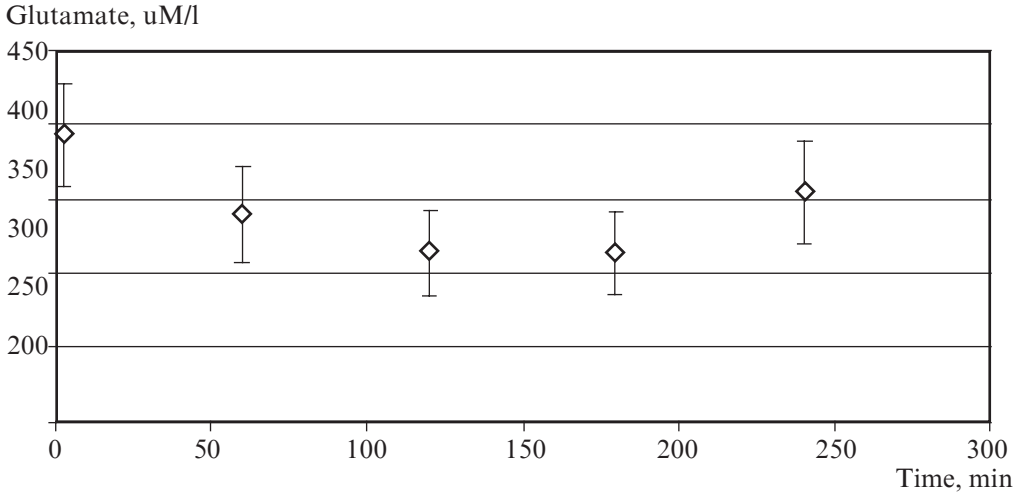

Fig. 1. Blood glutamate level during dialysis. Presented as average ± 95% CI

Note. Blood glutamate level during HD. Data is presented as mean ± 95% CI. In the first 3 hours after HD, there was a statistically-significant decrease in blood glutamate levels compared with baseline levels (* — $p<0.00001$). At the 4th hour, there was a statistically-significant increase in blood glutamate levels compared with the 3rd hour (# — $p<0.05$).

Table 2

Levels of various factors before and after HD. Presented as average ± S.D

Parameter	Pre-dialysis	Post-dialysis
Blood glutamate level	392.9±115.8	354.5±93.8
GOT	20.05±10.2	24.0±11.5
GPT	12.5±11.0	15.1±12.6
Ht	37.8±7.2	40.16±4.50
Urea	133±36	46±23
Cr	6.96±3.2	3.1±1.9
Glucose	118±67	173±58

Note. Blood levels of glutamate, GOT, GPT, Ht, urea, creatinine, and glucose before and after HD. Data is presented as mean ± S.D. GOT levels were higher after HD ($p<0.0001$), as were GPT levels ($p<0.0001$). Hct increased during HD ($p<0.05$), as did glucose levels ($p<0.0001$). Urea levels and creatinine levels both decreased during HD ($p<0.00001$).

As expected, hematocrit levels increased during HD (37.8±7.2 pre-HD vs. 40.16±4.5 post-HD, $p<0.05$). Urea levels decreased during HD ((133±36) mg/dL pre-HD vs. (46±23) mg/dL post-HD, $p<0.0001$), as did creatinine levels ((6.96±3.20) mg/dL vs. (3.1±1.9) mg/dL, $p<0.0001$). Glucose levels increased during HD ((118±67) mg/dL vs. (173±58) mg/dL, $p<0.0001$).

Discussion

It is well-known that excitatory amino acids such as glutamate activate calcium channels, causing an increased entry of calcium into the cell. This leads to a cascade that results in the activation of cellular proteolysis enzymes and damage to the cell membranes, leading to cell necrosis and apoptosis [14].

Human clinical trials examined the efficiency of several inhibitors of glutamate release and glutamate receptors antagonists, especially in the context of treating stroke. These experiments were aborted before their completion because of undesirable adverse events and even deaths that resulted from the drugs tested [9]. Therefore, to reduce glutamate neurotoxicity, it was suggested that we can regulate the levels of glutamate in the CSF and ECF by utilization of familiar mechanisms of glutamate transport from the brain to blood. In our lab, we previously examined various mechanisms to lower glutamate levels including by activation of beta 2 — adrenergic receptors and different kinds of hormones [21; 24–26].

The main purpose of this study was to examine whether HD can be used to filter the blood from glutamate, thereby reducing blood glutamate levels. It is known that many patients with chronic renal failure have an abnormal profile of blood amino acids [27]. In previous studies, pre-dialysis plasma amino acid levels in patients with end-stage kidney disease were significantly different compared with a healthy control group. Specifically, most of the essential amino acid levels were significantly reduced, while some of the non-essential amino acid levels were significantly elevated [27–29]. Patients with end-stage renal disease on HD were found to have elevated glutamate concentrations in the blood compared to a healthy control group [30].

Other studies have examined the effect of dialysis on blood amino acid levels in relation to dialysate outflow. It was demonstrated that peritoneal dialysis resulted in a loss of 1.5 to 4.6 grams of amino acids in 24 hours [31; 32], whereas HD can lead to a loss of up to 8 grams of amino acids [33]. This loss is mostly compensated for by one's diet. In another study that examined the loss of amino acids following HD with biocompatible membranes, a significant decrease in the total and essential amino acids was found in the plasma [34].

HD was also shown to result in an increase in protein catabolism[35]. It was found that the abnormal plasma amino acids profile in patients with end-stage renal disease was

further exacerbated following HD for most of the individual amino acids, and that dialysate amino acids losses are modulated by membrane characteristics and reuse [28]. These experiments however included only a small sample size, did not focus on glutamate, and did not examine the relative changes in concentration of amino acids during the dialysis process (they studied only pre and post-HD).

In this study we examined changes in glutamate levels during HD. We demonstrated that blood glutamate concentrations are higher in patients on HD compared with healthy controls. Glutamate levels were shown to decrease during the first hour of HD, stayed stable during the second and the third hour of HD, and appeared to rise slightly during the fourth hour. The size of the filter pores, blood flow rate, and gender did not seem to influence glutamate clearance.

As suggested by the blood glutamate level curve, the rate of change in glutamate levels during HD is not constant. The most prominent change in glutamate levels appears to occur during the first hour of HD. A concomitant measurement of urea levels demonstrates a stable decrease in urea levels during dialysis [36; 37], which emphasizes the unusual changes in glutamate levels. Since we used a constant flow of dialysate without recirculation, every point of time that the fluid entered the dialyser without glutamate, the possibility of over-saturating the dialysate was unlikely.

Furthermore, as the increase in glutamate levels appeared before discontinuation of HD, it would be incorrect to assume that a rebound of glutamate from body tissues could account for this phenomenon. One plausible explanation is that removal of urea from the plasma by HD exceeds its removal from the tissues. This delay in the removal of urea from the tissue creates an osmotic gradient between the cells and the plasma, which in turn leads to the development of the osmotic disequilibrium. Glutamate is a known organic osmolyte that plays an important role in osmotic adaptation [38; 39]. It is reasonable therefore to postulate that neurons secrete glutamate to the CSF and subsequently to the plasma in response to the hypoosmotic stress during HD. The late increase in glutamate levels may be a defense mechanism to counteract this disequilibrium syndrome. Thus, it would be expected that in chronic HD patients, the increase in blood glutamate levels would be more dramatic than that observed in new HD patients.

It should be stressed that if it is shown that the late increase in blood glutamate levels observed during the fourth hour of HD is unique to chronic HD patients, but does not occur in nonuremic patients, then the potential use of HD in decreasing brain glutamate levels after brain injury would be even more appealing. To evaluate this hypothesis, further examination of the glutamate clearance pattern in nonuremic patients during a conventional dialysis session, or of continuous therapy such as hemofiltration or hemodiafiltration, should be made.

Our data demonstrates that patients on HD had significantly lower levels of GPT activity, and a trend of lower levels of GOT activity, compared with controls. The activity of those enzymes increased significantly following HD. Previous studies showed that uremic patients have low levels of GOT and GPT activity [40], and that HD was associated with a significant increase of GOT and GPT activity [41]. The decreased activity of GOT and GPT in uremic patients, as well as their increased activity following HD, can be explained by a possible inhibition of transaminase activity by one or more of the accumulated molecules in the plasma. If this explanation is correct, then the increasing GOT and GPT activity observed in our study can be ascribed to the clearance of these potential inhibitory molecules during HD. Since GOT and GPT play a crucial role converting glutamate to the inactive metabolite 2-ketoglutarate [18], their

enhanced activity during HD may explain in part the observed decrease in blood glutamate levels.

A significant increase in glucose levels during HD was found in our study. This is likely because we used dextrose-containing dialysis fluids.

We observed no gender differences with regards to blood glutamate levels. In our previous clinical trials, in healthy volunteers, we demonstrated that blood glutamate levels are inversely correlated to estrogen and progesterone levels. It was shown that during the menstrual cycle in women, the increase in estrogen and progesterone levels was accompanied by a corresponding decrease in blood glutamate levels [42]. Similarly, other studies demonstrated that men have significantly higher blood glutamate levels compare with women [43], which may explain why women generally tend to have a better prognosis than men after traumatic brain injury and stroke. In this study, however, most of the women were post-menopausal. This fact likely accounts for lack of gender differences observed in our study.

Due to ethical considerations, we measured glutamate levels in the blood and not in the CSF. However, previous studies with magnetic resonance spectroscopy confirmed that the increase in glutamate levels in the brain parenchyma after middle cerebral artery occlusion (MCAO) is inhibited after oxaloacetate-mediated GOT activation [5–7]. Teichberg and colleagues used microdialysis probes in rats to demonstrate that the artificial decrease in blood glutamate following the administration of blood glutamate scavengers results in a decreased concentration in glutamate levels in brain ECF in rats [14]. Castillo and colleagues further showed that lower blood glutamate levels and higher levels of GOT were associated with a better neurological outcome in patients after ischemic stroke [5–7]. Thus, it is reasonable to suggest that glutamate reduction by dialysis, as seen in our study, may be a promising method of reducing glutamate levels in the CSF and improve the neurological outcome after brain insults in humans.

Due to technical difficulties, glutamate levels were not measured in the dialysate. Therefore we were not able to calculate glutamate clearance accurately, which was only estimated by glutamate blood levels. Another important limitation of this study is that we examined only patients with end stage kidney disease. In order to assess the effect of dialysis on patients with brain injury, further study is required with non-uremic patients.

Previous studies done by our group and others have shown that pharmacologically reducing blood glutamate levels with glutamate scavengers (such as oxaloacetate and pyruvate), limits glutamate neurotoxicity and provides better neurological outcomes following various brain insults, particularly traumatic brain injury [14; 19–21; 44–53]. Unfortunately, despite the fact that these treatments have been shown to be effective in animal models of stroke, traumatic brain injury and subarachnoid hemorrhage, their use in humans is limited by FDA restrictions. Most of these studies, based on rat models of traumatic brain injury, have shown blood glutamate reduction to be most effective when applied within the first 120 min post injury [19; 20]. This study, introduces a proof of concept regarding the use of non-pharmacologic measures such as hemodialysis and possibly other modes of renal replacement therapy such as hemofiltration in order to decrease blood and brain glutamate levels without pharmacological intervention. Thus, acute HD treatment for severe head trauma, initiated in the initial hours post injury, may improve neurological outcomes by limiting secondary brain damage in the first hours post injury, acting by the mechanisms described above.

In summary, we demonstrated the pattern and rate of glutamate clearance during HD. Glutamate levels were shown to decrease during the first hour of HD, and slightly in-

crease during the fourth hour of HD. A concomitant increased of GOT and GPT activity was shown during HD. HD may be a promising method of reducing blood glutamate levels (and subsequently brain glutamate levels) after traumatic brain injury. Although dialysis is known to induce hypotension [54–56], which may limit its use in hemodynamically unstable patients, our results suggest that other dialysis methods which have less effect on blood pressure (such as low-efficiency dialysis) may be equally effective in reducing blood glutamate levels. Further studies are required to assess the efficacy of these techniques on reducing blood glutamate levels.

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NEW THERAPEUTIC STRATEGIES IN TREATMENT OF POSTOPERATIVE NAUSEA AND VOMITING

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НОВЫЕ ТЕРАПЕВТИЧЕСКИЕ СТРАТЕГИИ В ЛЕЧЕНИИ ПОСЛЕОПЕРАЦИОННОЙ ТОШНОТЫ И РВОТЫ

Актуальность. При отсутствии лечения у трети пациентов, которым проведены хирургические операции, развиваются послеоперационная тошнота и/или рвота (PONV). Предотвращение послеоперационной тошноты и рвоты может улучшить степень удовлетворения среди уязвимых пациентов. Мы предположили, что предоперационная тревога может увеличить заболеваемость PONV. Цель заключалась в том, чтобы оценить, будет ли введение бензодиазепина до операции уменьшать заболеваемость PONV.

Методы. Исследовательскую группу составили 130 женщин (ASA I и II), которые планировали пройти дилатацию и кюретаж. Женщины распределялись случайным образом в две исследовательские группы в соответствии с типом введения анестезии (с мидазоламом и без него).

Результаты. Мидазолам получили 68 женщин, а 62 — нет. Пациенты, получавшие мидазолам, чувствовали себя более комфортно («Дружелюбие», p=0,005, и «Доброжелательность», p=0,01) и имели меньшую послеоперационную усталость (p=0,04), чем группа, не получавшая мидазолам. У пациентов, получавших мидазолам, в первые 4 ч после операции было значительно меньше рвотных эпизодов, чем у пациентов, не получавших мидазолам (0,1± ±0,2 против 0,3±0,6 соответственно, p=0,003).

Выводы. Мидазолам уменьшает заболеваемость PONV и улучшает комфорт пациента. Мы предлагаем, чтобы мидазолам регулярно включался в протокол анестезии для краткосрочных гинекологических процедур (дилатация и кюретаж).

Ключевые слова: беспокойство, мидазолам, послеоперационная тошнота и рвота.